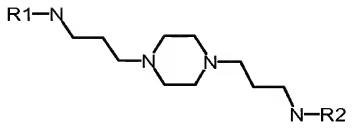
LISTING OF CLAIMS READABLE ON ELECTED SPECIES

1. (previously presented) A composition for transfecting an siRNA into a cell in vitro comprising: an amphipathic compound, a polyvinylamine, and said siRNA.
2. (previously presented) The composition of claim 1 wherein the amphipathic compound has the structure comprising:



wherein R1 and R2 consist of C6-C24 alkenes.

3. (original) The composition of claim 2 wherein R1 and R2 of the amphipathic compound are the same.
5. (previously presented) A process for transfecting an animal cell *in vitro* with a siRNA comprising: adding to the cell in a solution a composition comprising an amphipathic compound, an effective amount of a polyvinylamine, and a siRNA, wherein the composition facilitates entry of the siRNA into the cell.
9. (previously presented) The process of claim 5 wherein the animal cell is a mammalian cell.

Remarks

Double Patenting and Rejection of the claims under 35 USC §103:

Claims 1-3 and 5-9 have been rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent 5,744,335 in view of Wolfert et al. (Bioconjugate Chemistry 1999) and Leake et al. (US 2004/0224405).

Claims 5, 6, and 9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al. (U.S. Patent 5,744,335) in view of Wolfert et al (Bioconjugate Chem. 1999) and Pollard et al. (J Biol Chem, 1998, 27:7507-7511).

Applicants respectfully disagree. The Action states on page 5 that Wolfert et al. teaches that polyvinylamine efficiently condenses nucleic acids and forms small complexes with good extracellular stability. It is the Applicants' opinion that the condensation of plasmid DNA and formation of small complexes with good extracellular stability are not predictive of siRNA transfection capability. Plasmid DNA is several thousand base pairs long and in solution has a very large hydrodynamic radius (effective size). The long nucleic acid tends to occupy a large space in solution because of charge repulsion between the negative charges along the entire length of the nucleic acid. Nearly any polycation of sufficient length and charge density can condense plasmid DNA by neutralizing this charge repulsion (WO 0003694, page 2 line 5 to page 4 line 15). However, not every polycation is useful in transfection. In fact, most polycations are not good transfection reagents. In contrast, siRNA, whose length is less than 50 base pairs in length, while forming complexes with polycations, is not effectively condensed by polycations in the way that larger nucleic acids are condensed. Therefore, condensation of plasmid DNA by a polymer is not an effective measure of the likelihood of the polymer being an effective siRNA transfection reagent.

The Action states on page 5 that motivation to used polyvinylamine in combination with siRNA is provided by Wolfert et al. because Wolfert et al. teach that the use of polyvinylamine results in small complexes that are stable in circulation, can undergo extravasation in the target tissue, and can easily enter into the nucleus of target cells. Applicants have amended to claims to specific in vitro delivery. The formation of small complexes that are stable in circulation and can undergo extravasation is irrelevant to *in vitro* transfection.

The Action states on page 7 that Wolfert et al. teach that small DNA/polyvinylamine complexes are stable and capable of entering the nucleus due to their small size, and therefore such complexes mediate efficient transcription and are suitable for intranuclear delivery. However, Applicants have claimed a complex for transfection, not for efficient transcription or intranuclear delivery. For a complex already present in the cytoplasm of a cell, small size may be important for import into a nucleus. However, while small size my be important, or even necessary, for intranuclear transport, it is not sufficient for transfection. Transfection requires attachment of the complex to the cell, internalization of the complex, transport of the complex across a cell membrane (either the plasmid membrane or an endosomal/lysosomal membrane), and transport of the nucleic acid to and into the nucleus (for nucleic acid to be that is to transcribed). That a complex is of a sufficient size to accomplish one of these steps does not suggest that the complex is competent to accomplish all of these steps. Applicants respectively reiterate that Wolfert et al. directly state that DNA/polyvinylamine complexes "gave *no* (ital. added) significant spontaneous transfection when applied to 293 cells in vitro". Thus, Wolfert et al. explicitly teach away from the use of polyvinylamine for transfection. Further, Applicants respectfully point out that siRNAs are not transcribed and that delivery to the nucleus is not a requirement for effective transfection of siRNA. Thus, formation of complexes that mediate efficient transcription and are suitable for intranuclear delivery are not requirements for siRNA transfection.

It appears that the Action maintains that because DNA/polyvinylamine complexes are small in size, that it would have been obvious to use polyvinylamine as a component of a transfection reagent. With this response, Applicants have filed a Declaration under 37 C.F.R. 1.132 showing the histone/lipid/plasmid DNA complexes, as taught by Wolff et al., are large compared to the polyvinylamine/DNA complexes taught by Wolfert et al. The Declaration further states that larger complexes rather than smaller complexes tend to work better for *in vitro* DNA transfection than smaller complexes. Therefore, the formation of small complexes as taught the Wolfert et al. can not be considered to be suggestive that polyvinylamine would form an effective transfection product when combined with the teaching of '335.

Finally, Applicants further show, in a Declaration under 37 C.F.R. 1.132, that polyvinylamine/1,4-disubstituted piperazine/DNA complexes are not effective plasmid DNA

transfection complexes. Conversely, histone/1,4-disubstituted piperazine/siRNA complexes are not effective siRNA transfection complexes. Therefore, histone and polyvinylamine have patentably distinct properties. Furthermore, while '335 teaches that histone/1,4-disubstituted piperazine may be an effective oligonucleotide transfection composition, the data in the declaration clearly show that histone/1,4-disubstituted piperazine is not an effective olionucleotide (siRNA) transfection reagent. Therefore, the finding that polyvinylamine/1,4-disubstituted piperazine does form an effective siRNA transfection composition must be considered to be an unexpected result.

In view of the arguments presented above, Applicants respectfully request reconsideration of the rejections.

New Claims:

Support for new claim can be found in claim 1 as originally filed. Support for new claims 11-20 can be found in the specification on page 6 lines 24-34, page 9 lines 20-15 (structure #1 containing an acyl segment of a fatty acid), and FIGs. 3-6.

The Examiner's rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-3, 5, and 9-20 should be allowable.

Respectfully submitted,

/Kirk Ekena/

Kirk Ekena, Reg. No. 56,672
Mirus Bio Corporation
505 South Rosa Road
Madison, WI 53719
608-238-4400

I hereby certify that this correspondence is being transmitted to the USPTO on this date: 05/07/2008 .

/Kirk Ekena/
Kirk Ekena